Pediatric Drug Development: Regulatory Expectations

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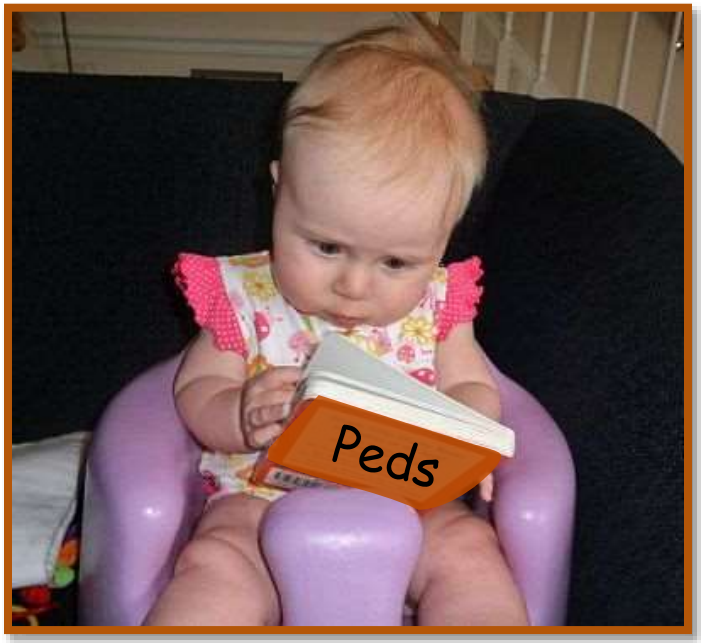
Disclosure Statement

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Objectives

- Understand the basics of the U.S. Pediatric Drug Development Laws
- Learn the basic Regulatory Expectations
- Learn how to Avoid Common Pitfalls



Acronyms

- BPCA Best Pharmaceuticals for Children Act
- EOP2 End of Phase 2
- FDAAA Food & Drug Administration Amendments Act
- FDASIA Food & Drug Administration Safety & Information Act
- PeRC Pediatric Review Committee
- PMHS Pediatric & Maternal Health Staff
- PPSR Proposed Pediatric Study Request
- PREA Pediatric Research Equity Act
- PSP Pediatric Study Plan
- WR Written Request

TOP 10

Pediatric Drug Development Questions

Question 10

Who are pediatric patients?

Pediatric Patients

- Age range depends on context
  - Labeling regulations for prescription drugs: 0 to 16 years old [21 CFR 201.57(c)(9)(iv)]
  - Clinical trials: *Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. [21 CFR 50.3(o)]

Question 9

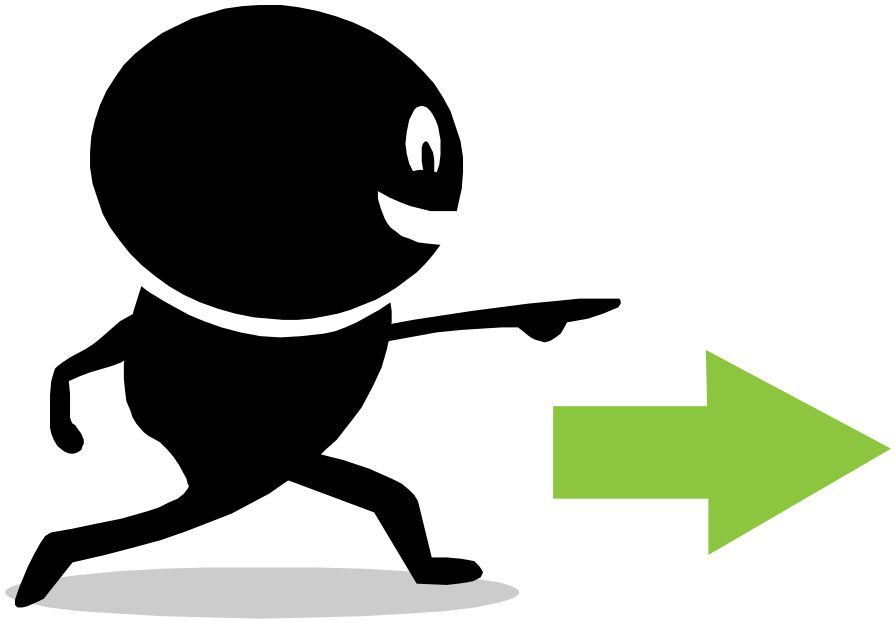
Why should we enroll children in clinical trials?

Pediatric Drug Development – *The Past*

Choices for Pediatric Practitioners

- **Not treat** children with potentially beneficial medications because the medications were not approved for use in children
- **Treat** with medications based on adult studies with **limited** or anecdotal pediatric experience (off-label use)

The Present



Pediatric Drug Development
General Principles

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

- Give pediatric patients products that have been appropriately evaluated for them
- Product development programs should include pediatric studies when anticipate pediatric use

Why We Need Pediatric Trials

- Children get sick - they need medication
- Children should have access to medicines that have been properly evaluated for use in the intended population

- Thoughtful drug development and inclusion of pediatric patients in trials is critical to public health

Question 8

What are the main U.S. pediatric drug development laws?

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
- Title V of FDA Safety and Innovation Act (FDASIA)

PREA and BPCA

- **Pediatric Research Equity Act (PREA)**
  - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients (Pediatric Assessment)

- **Best Pharmaceuticals for Children Act (BPCA)**
  - **Provides a financial incentive** to companies to voluntarily conduct pediatric studies

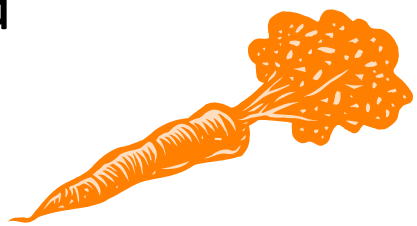
PREA vs. BPCA

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled



Ultimate Goal of PREA and BPCA

PREA  ***BPCA***

New Pediatric Labeling

to encourage appropriate use of medications

to treat pediatric patients

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
- Title V of FDA Safety and Innovation Act (FDASIA)

Question 7

When does PREA apply?

Pediatric Research Equity Act (PREA)

- Is triggered by an application for:
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration
  - New active ingredient

Question 6

What is a Pediatric Assessment?

PREA: Pediatric Assessment

- **Data** from pediatric studies using appropriate formulations for each age group and other data
  - **To assess the safety and effectiveness** of a drug/biologic for the claimed indications in all relevant pediatric subpopulations AND
  - **To support dosing and administration** for each pediatric subpopulation for which the drug or biological product is safe and effective

Question 5

How does my company discuss with the FDA ahead of time our plans to fulfill PREA?

Pediatric Study Plan (PSP)

- Outline of the pediatric study(ies) the sponsor plans to conduct
- The intent of the PSP:
  - Encourage sponsors to identify pediatric studies as early as possible in product development
  - When appropriate, to conduct those studies prior to submitting the NDA/BLA

Timing of a PSP Submission (current)

- If End of Phase 2 (EOP2) Meeting will occur
  - PSP must be submitted within 60 days
- If no EOP2 Meeting to occur, then PSP should be submitted as early as possible and at a time agreed upon by FDA and sponsor
  - FDA strongly encourages PSP to be submitted prior to initiation of Phase 3 studies
  - PSP must be submitted no later than 210 days prior to submission of application

Question 4

What if our company believes we should wait to do pediatric studies until additional adult data is available?

PREA: Pediatric Deferral

- The submission of some or all assessments may be deferred until a specified date after approval

PREA: Deferral Criteria

- The drug/biologic is ready for approval for use in adults before pediatric studies are complete OR
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected OR
- There is another appropriate reason for deferral (e.g., scientific issues exists regarding study design or endpoints)

Question 3

What if the disease our product is treating doesn't exist in pediatric patients?

PREA: Pediatric Waiver

- The requirement for assessments may be waived
- May be a full waiver (all pediatric ages) or partial waiver (a subset of the pediatric population)

PREA: Waiver Criteria

- Necessary studies are impossible or highly impracticable OR
- Evidence strongly suggests the drug/biologic would be ineffective or unsafe OR
- Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used by a substantial number of pediatric patients OR
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed (partial waiver only)

PREA: Deferrals and Waivers

- FDA review divisions and sponsors should discuss PREA requirements early in the drug development process
- PSP needs to include plans to request deferrals, waivers or partial waivers with supporting data
- Final deferral and waiver decisions are made at the time of NDA/BLA approval

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
- Title V of FDA Safety and Innovation Act (FDASIA)

Question 2

How does the incentive under BPCA work?

Best Pharmaceuticals for Children Act (BPCA)

- Provides for **voluntary** pediatric drug studies via a Written Request (WR)
- Reflects need for information that may produce health benefits in the pediatric population
- Authorizes FDA to **request pediatric studies of approved and/or unapproved indications**

BPCA: Written Request

- A sponsor may request the FDA to issue a WR by submitting a Proposed Pediatric Study Request (PPSR)
- PPSR should contain:
  - Rationale for studies and study design
  - Detailed study design
  - Appropriate formulations for each age group
- FDA may issue a WR without a PPSR
- Sponsors who submit studies to fulfill a WR may be eligible to receive pediatric exclusivity

BPCA: Pediatric Exclusivity

- If the terms of the WR have been met and studies were conducted using good scientific principles, the company is awarded an additional 6 months of exclusivity
  - Exclusivity attaches to all existing marketing exclusivities and patents for the drug moiety (initial WR)
  - Pediatric exclusivity does not require positive pediatric studies (initial WR)
- Granting of exclusivity is reviewed by the FDA Pediatric Exclusivity Board

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
- Title V of FDA Safety and Innovation Act (FDASIA)

FDASIA: Selected Changes

- Permanently reauthorized PREA & BPCA
- Changes to PREA
  - New ability to provide extensions for the submission of deferred studies
  - Issuance and publication of non-compliance letters
  - Requirement to submit Pediatric Study Plans
- Changes to BPCA
  - Neonates must be addressed in Written Requests

Question 1

What are common mistakes you see drug companies make with respect to these pediatric laws?

Common Pitfalls

Common Pitfall #1

- A drug company plans to submit a NDA for a product intended to treat a respiratory condition that occurs commonly in both adults and children.
- The company only wants approval for use of the product in adults. Therefore, the company does not plan to study their product for use in children.

Common Pitfall #1: Reality

- The company may still be required to study their product for use in pediatric patients
- PREA is triggered by an application for (at least 1 criteria):
  - a new indication
  - a new dosage form
  - a new dosing regimen
  - a new route of administration
  - a new active ingredient

Common Pitfall #2

- A drug company understands they are required to submit their PSP within 60 days of their EOP2 Meeting.
- The company believes that because they don't have their adult studies completed yet, and therefore they can't finalize their pediatric study designs, the PSP would be mostly blank.

Common Pitfall #2: Reality

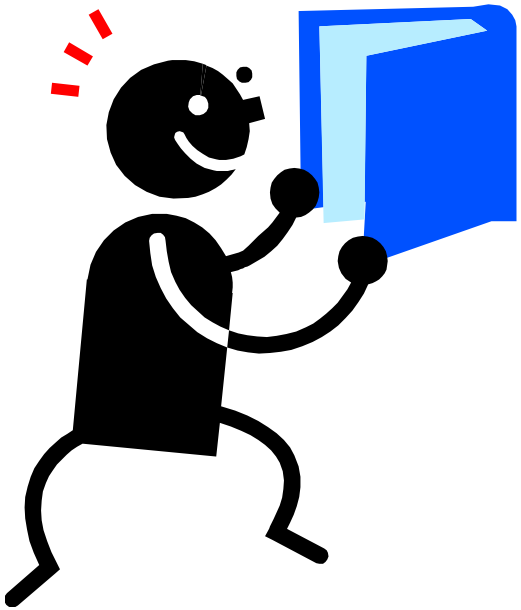
- FDA understands that in some situations, it may be premature to include detailed pediatric study designs due to the need for additional data.
- Nonetheless, the PSP should be completed and relevant information, as available, included.

Pediatric Study Plan: Contents

1) Overview - Disease Condition
2) Overview - Drug/Biologic Product
3) Plan for Extrapolation
4) Plan to Request Waiver(s)
5) Summary of Planned Nonclinical and Clinical Studies
6) Pediatric Formulation Development
7) Nonclinical Studies
8) Clinical Data to Support Design and/or Initiation of Studies
9) Planned Pediatric Clinical Studies
10) Timeline of the Pediatric Development Plan
11) Plan to Request Deferral
12) Agreements with Other Regulatory Authorities

Pediatric Study Plan: More Information

- Draft Guidance for Industry Pediatric Study Plans, July 2013: http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/UCM360933.pdf



What Happens After a PSP is Submitted?

Sponsor submits initial PSP

(Day 0)

↓

FDA provides comments

(Day 90)

↓

Sponsor submits revised initial PSP

(Day 180)

↓

FDA confirms agreement with initial PSP

(Day 210)

Common Pitfall #3

- A drug company plans to seek approval for its product, Awesometablet.
- In creating its PSP, the company plans to request a partial waiver for patients <6 years of age.
  - Patients <6 years of age could benefit from the medicine.
  - But Awesometablet exists only in tablet form, and children <6 years of age cannot swallow a tablet the size of Awesometablet.

Common Pitfall #3: Reality

- Even if children <6 years of age are unable to swallow Awesometablet, PREA requires an age-appropriate formulation.
- A partial waiver will be appropriate only after reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Common Pitfall #4

- Wonderdrug is approved only for Indication A in adults.
- When Wonderdrug was approved for Indication A, PREA was triggered.

Indication	Approved	Required under PREA
Indication A	Adults	Pediatrics

Common Pitfall #4, continued

- There may be off-label use for Indication B, but pediatric studies for Indication B cannot be required under PREA

Indication	Approved	Required under PREA
Indication A	Adults	Pediatrics
Indication B	----	----

Common Pitfall #4, continued

- The drug company wants a Written Request to study only Indication A in pediatric patients.

Sponsor's Request

Indication	Approved	Required under PREA
Indication A	Adults	Pediatrics
Indication B	----	----

- The drug company believes that this is the only indication that would be in a Written Request because
  - Indication A is the only approved use
  - Pediatric studies are only required for Indication A

Common Pitfall #4: Reality

- A Pediatric Written Request may contain studies for **both** approved and unapproved indications (Indications A and B in this case.)

Indication	Approved	Required under PREA
Indication A	Adults	Pediatrics
Indication B	----	----

Written Request

Common Pitfall #4: Reality, continued

- Completion of all studies that are outlined in the Pediatric Written Request is required to fulfill the Pediatric Written Request
- May include clinical and non-clinical studies

Common Pitfall #5

- A drug company assumes pediatric efficacy trials are required to approve an NDA or supplement that includes a pediatric indication.

Common Pitfall #5: Reality

- A pediatric efficacy trial is not necessarily required
- Efficacy for some or all of the pediatric patients may be able to be extrapolated from adequate and well-controlled adult trials
- Pediatric safety and dosing information would still be required

Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, …pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."

Pediatric Research Equity Act of 2007 (Title IV FDA Amendments Act 2007)
Emphasis added

Extrapolation of Efficacy

- Pediatric efficacy may be able to be extrapolated
  - Disease pathophysiology and the effect of the drug must be the same
- At a minimum, pediatric PK (to determine dosing) and safety data are required/requested

Pediatric Study Planning & Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

No to either

Yes to both

And the algorithm continues from there

More Information on Extrapolation

- Pediatric Clinical Pharmacology, including Extrapolation
  - General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Draft Guidance for Industry, December 2014 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf

Pediatric Labeling

Common Pitfall #6

- A drug company is seeking FDA approval for a medicine to treat ear infections in adult and pediatric patients.
- This drug company studied their product in both adult and pediatric patients and found it was safe and effective for both populations.
- This company, in their proposed labeling, has included all the pediatric information, including the study results, in the Pediatric Use subsection (8.4).

Common Pitfall #6: Reality

When the indication **is** approved for children:
Pediatric information is located throughout the labeling

Common Pitfall #6: Reality, continued

When the indication **is not** approved for children:

- Most pediatric information is located in specific labeling sections
  - Physician's Labeling Rule: Use in Specific Populations – 8.4 Pediatric Use
- Pediatric safety information that rises to the level of warning, precaution, contraindication
  - Incorporated in those sections

Common Pitfall #6: Reality, continued

- If pediatric studies are waived (full or partial) because the evidence strongly suggests the drug/biologic would be ineffective or unsafe, that information must be included in labeling.

More Information on Pediatric Labeling

- Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, Draft Guidance for Industry, February 2013

  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf

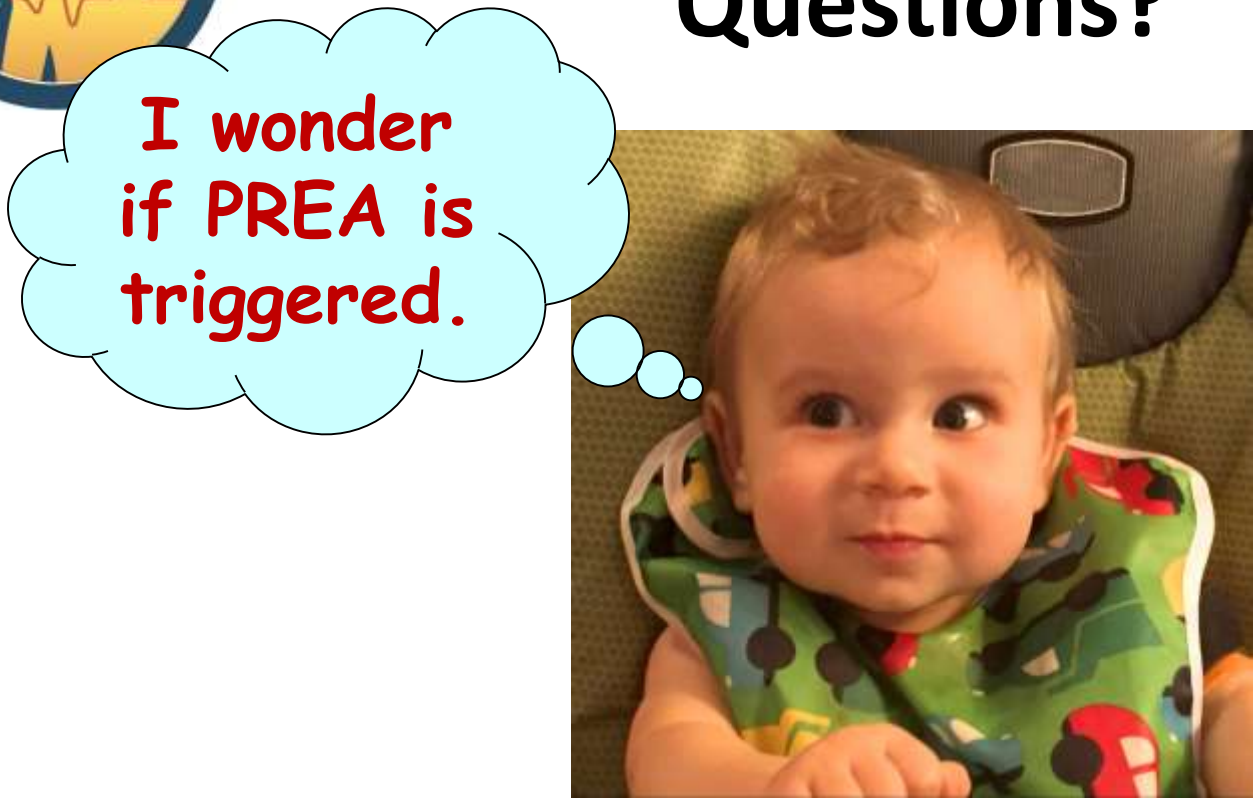
Additional Information

- Pediatric Drug Development
  - Guidance for Industry: E11, Clinical Investigation of Medicinal Products in the Pediatric Population
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
- Pediatric Ethics
  - 21 CFR 50 Subpart D

Closing Thoughts

- Pediatric drug development is different than drug development in adults
- There are pediatric drug development requirements stipulated under PREA
- Voluntary pediatric studies may be conducted under BPCA
- Plan early, plan often, and expect that the best-laid plans may change

Questions?



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The End

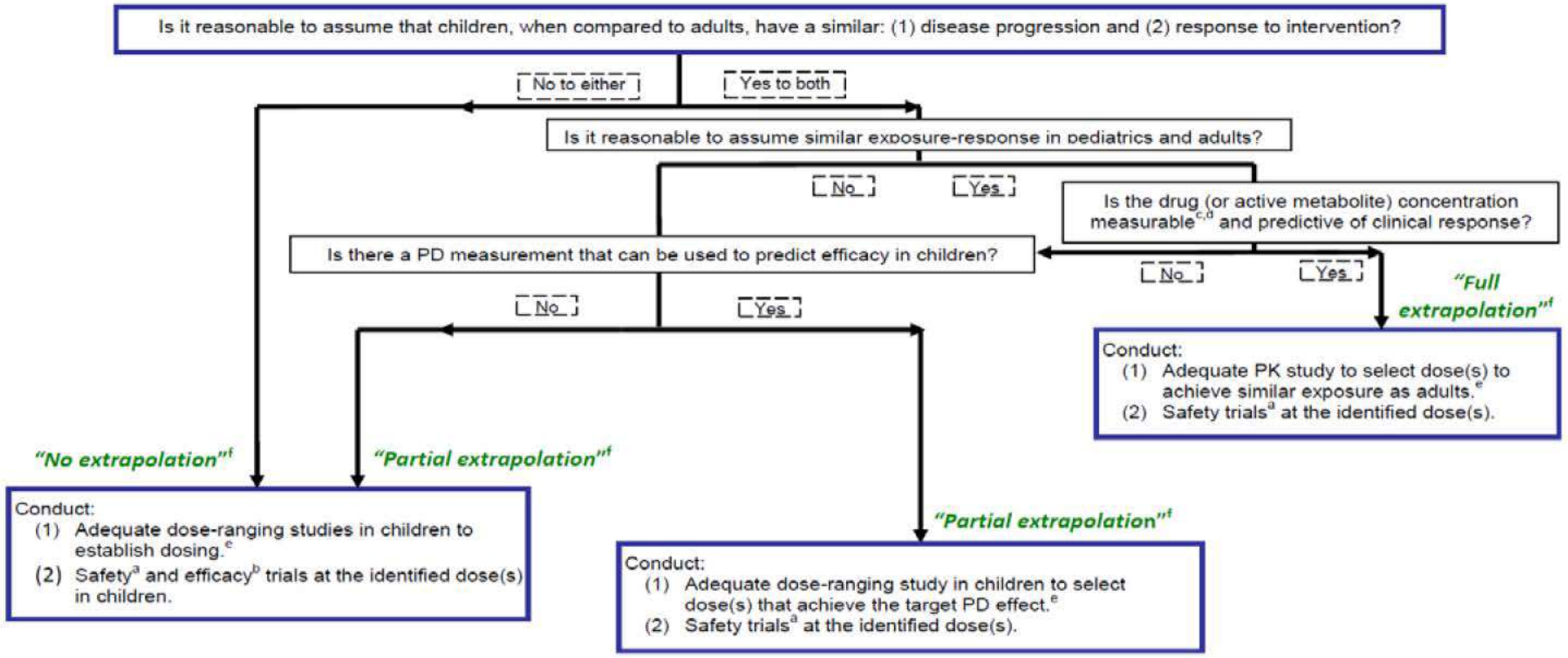
Back-up slides

PREA: Deferral Requirements

The sponsor must submit

- ✓ Certification of the grounds for deferring the assessments AND
- ✓ A Pediatric Study Plan AND
- ✓ Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time AND
- ✓ A timeline for the completion of such studies

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.